Predicting the effect of vaccination on the transmission dynamics of heartwater (*Cowdria ruminantium* infection)

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Abstract

We used a mathematical description of the transmission dynamics of the tick-borne infection *Cowdria ruminantium* in commercial beef enterprises in Zimbabwe to consider the potential impact of a candidate vaccine to prevent heartwater. The important characteristics of the vaccine were (1) a delay in development of full protection, (2) prevention of clinical disease but not of infection and (3) a waning period of protection in the absence of challenge. We considered three different scenarios in which the vaccine might be used: prophylactically in susceptible cattle prior to the introduction of infection into a herd; in susceptible cattle in the face of an epidemic (i.e., when the infection is introduced and disease is first noticed); and at equilibrium (i.e., when parasite, vector and host have been co-existing for some time). The epidemic rise in infection was modelled assuming two different patterns (i.e., resulting from slow and fast increases in tick challenge).

Vaccination (administered both in the face of an epidemic and prophylactically) reduced and delayed the peak of the epidemic. With insufficiently frequent revaccination, this can result in the epidemic occurring during a period of susceptibility, so that the benefit derived from a more-efficacious vaccine is lower than that from a less-efficacious vaccine. A vaccine of only 30% or 50% efficacy (if given to the whole herd) can have important effects on both morbidity and mortality if administered with sufficient frequency. However, a highly efficacious vaccine (e.g., 90%) can have only minimal effect if revaccination occurs too infrequently – especially if the

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epidemic of disease occurs when tick challenge is high and vaccination-related immunity has waned. There was a fairly consistent pattern of decreasing returns on increasing protection, although this was reversed in the situation of annual vaccination undertaken prophylactically combined with an epidemic of infection that occurred when the tick challenge was relatively low.

Vaccination in equilibrium situations was most beneficial at low and intermediate tick challenges. There was very little effect of vaccination in high-transmission areas regardless of vaccine efficacy and/or frequency of revaccination because most animals were infected during periods of innate or maternally derived immunity (i.e., under endemic stability).

Our results suggest that where relatively high tick challenge can be achieved and consistently maintained, vaccination may be used in susceptible herds to minimise losses in a policy of transition to endemic stability. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

There is a complex of tick-borne diseases (TBD: principally heartwater, theileriosis, anaplasmosis and babesiosis) which severely constrains livestock production throughout sub-Saharan Africa (Young et al., 1988; Mukhebi et al., 1992, 1999; Bezuidenhout et al., 1994; Perry and Young, 1995). Control of these diseases traditionally relies heavily on frequent application of acaricides which are expensive, toxic and whose use is contrary to current ecological concerns. Vaccines are currently either available or under advanced stages of development for all these infections, and there is an urgent need to investigate the impact of their use on transmission dynamics and livestock production economics. In particular, we require tools to aid the design of cost-effective, integrated, control programmes. Without conducting long-term, expensive field trials, the only way of exploring these aspects is through predictive, quantitative models.

We developed such a framework by considering a single infection (heartwater) which is an infectious disease of ruminants caused by the rickettsial organism *Cowdria ruminantium* and is transmitted by ixodid ticks of the genus *Amblyomma* (and possibly through vertical transmission) (reviewed by Camus et al., 1996; Deem et al., 1996b). Heartwater is found throughout most of sub-Saharan Africa and neighbouring islands and on at least three islands in the Caribbean. It is the actual and potential geographical spread of the vector and the consequent risk of large-scale epidemics that has directed recent attention to this infection (Burridge, 1997).

The epidemiology of heartwater varies greatly between different combinations of agro-ecological zones and production systems. The introduction of *C. ruminantium* infection into a previously unexposed population results in an epidemic of heartwater with high mortality (Norval, 1978, 1979; Lawrence and Norval, 1979; Norval and Lawrence, 1979). However, in circumstances where the vector density is high and host infection is common and occurs early in life, morbidity and mortality of hosts are greatly reduced. This latter situation has been termed endemic stability (Norval et al., 1992; Perry et al., 1992; Perry and Young, 1995; Deem et al., 1996b; O'Callaghan et al., 1998), and represents an ecologically sustainable relationship between host, vector and environment. Given this

range of epidemiological states, the efficacy and impact of a vaccine must be evaluated under different circumstances, and we have considered three representative conditions of vaccine use: (1) prophylactic vaccination (i.e., vaccinating highly susceptible cattle before the introduction of *C. ruminantium* infection), (2) vaccination in the face of an epidemic (i.e., introduction of vaccination in a herd or herds on the first appearance of disease), and (3) vaccination at endemicity (i.e., introduction of vaccination when the infection is already at a [mathematically] stable equilibrium).

A problem exists in integrating the terminology of TBD epidemiology and transmission dynamic modelling. For example, a model of a dynamic system may be at a (mathematically) stable equilibrium, but the disease burden predicted is such that it is agriculturally/economically unsustainable and therefore considered "unstable". Equally, a situation where infection pressure is suppressed only by intensive and sustained vector-control efforts may be reflected by a consistently low incidence of disease and again modelled as having reached a mathematical equilibrium but is considered epidemiologically unstable by virtue of the potential for increased transmission of infection should the control efforts break down. In contrast, endemic stability implies stability in terms of (i) transmission dynamics, (ii) vector challenge and (iii) agro-economical sustainability. We differentiate these concepts by referring to stability and sustainability of epidemiological states while "equilibrium" is only used to refer to a dynamic (mathematical) equilibrium.

Vaccines that induce solid, sterile, long-lasting immunity are usually only available for relatively simple and homogeneous pathogens. Typically, vaccines against more complex and heterogeneous organisms are protective only against disease rather than against infection. Most vaccines developed against tick-borne diseases to date have been variants of the "infection and treatment" method, using live organisms and chemoprophylaxis sequentially (Radley et al., 1975; van der Merwe, 1987; Tjornehoj et al., 1997). Although efficacious, such vaccines have concomitant problems of vaccine-induced disease, cold-chain and monitoring requirements and heterogeneity in the level of protection (du Plessis et al., 1989; Morzaria, 1996). However, a new generation of inactivated vaccines for heartwater is currently being developed (Mahan et al., 1995, 1998; Martinez et al., 1994, 1996) which are safer and more predictable but which may induce immunity of shorter duration in the absence of challenge.

There is already considerable theory regarding the population-level influence of sterile, long-lasting, vaccine-induced immunity (Anderson and May, 1991; Grenfell and Dobson, 1996), relatively little attention has been paid to the optimal use of shorter-acting vaccines which protect against disease (and permit infection) (Medley, 1994). There has also been relatively little attention paid to vaccination in dynamically changing situations (such as in the face of an epidemic) compared to static (equilibrium) situations. Although the complete characteristics of a future heartwater vaccine have not yet been fully elaborated, we have incorporated a theoretical vaccine with three characteristics thought to be typical of inactivated vaccines in general: (1) the existence of a lag period between primary vaccination and the development of immunity, (2) a limited duration of immunity, and (3) less than 100% vaccine efficacy (i.e., the proportion of animals vaccinated that is protected from disease). We emphasise that the parameter values are used to define a set of specific characteristics for a theoretical vaccine and may be

considered only broadly representative of the heartwater vaccines under development (Mahan et al., 1998).

Overarching the consideration of epidemiological states and vaccine characteristics is the importance of the eco-agricultural production system. Whilst heartwater is known to be an important disease in sheep, goats and cattle across a variety of agro-ecological zones and production systems, we chose to concentrate on large-scale commercial beef herds in Zimbabwe – each of which may be considered as a relatively discrete livestock and tick population under uniform disease-control management (and, hence, subject to a uniform vaccination policy). We used a mathematical, transmission-dynamics model to provide an assessment of the epidemiological impact of vaccination. Within this mechanism we concentrated on different epidemiological situations with different vaccine efficacies. The quantitative results have already been used in an economic assessment of the vaccine (Mukhebi et al., 1999). We also draw general conclusions regarding the use and evaluation of vaccines of this nature.

2. Materials and methods

2.1. Incorporating vaccination in a transmission model framework

The mathematical model that we used is based on a previous model for theileriosis (Medley et al., 1993), and is described in detail by O'Callaghan et al. (1998). Briefly, the transmission model's framework has three components: a deterministic, compartmental model of *C. ruminantium* infection transmission within a host population; a mammalian/host demographic model; and a model of the tick/vector population dynamics. The original model did not include vaccination. To facilitate understanding of how vaccination was integrated into the model, a summary of the *C. ruminantium* infection transmission model is provided in the Appendix A and depicted graphically in Fig. 1. The structure by which the hypothetical vaccine has been incorporated is intended to approximate the behaviour of an inactivated vaccine: infection is not established on vaccination and vaccination protects against disease but not against initial infection.

Vaccination was incorporated within the compartmental model by the addition of three mutually exclusive host categories. These additional categories were based on current understanding of the immunological response to vaccination and the nature and duration of protection conferred on subsequent challenge, all within the natural history of infection. More specifically, the assumptions made concerning the vaccination categories are as follows:

Primary inoculation; ***h***. The primary inoculation category attempts to account for the delay in a host acquiring full immunity over an immunisation course (the induction period). We have chosen to model this period as a separate class rather than as a time-delay for two reasons: first, to acknowledge that the process of acquisition of primary immunity is progressive rather than instantaneous, and second, to allow us to incorporate pulse vaccination without the complication of interacting time delays. Animals in this category have been vaccinated for the first time, and have yet to develop immunity or to
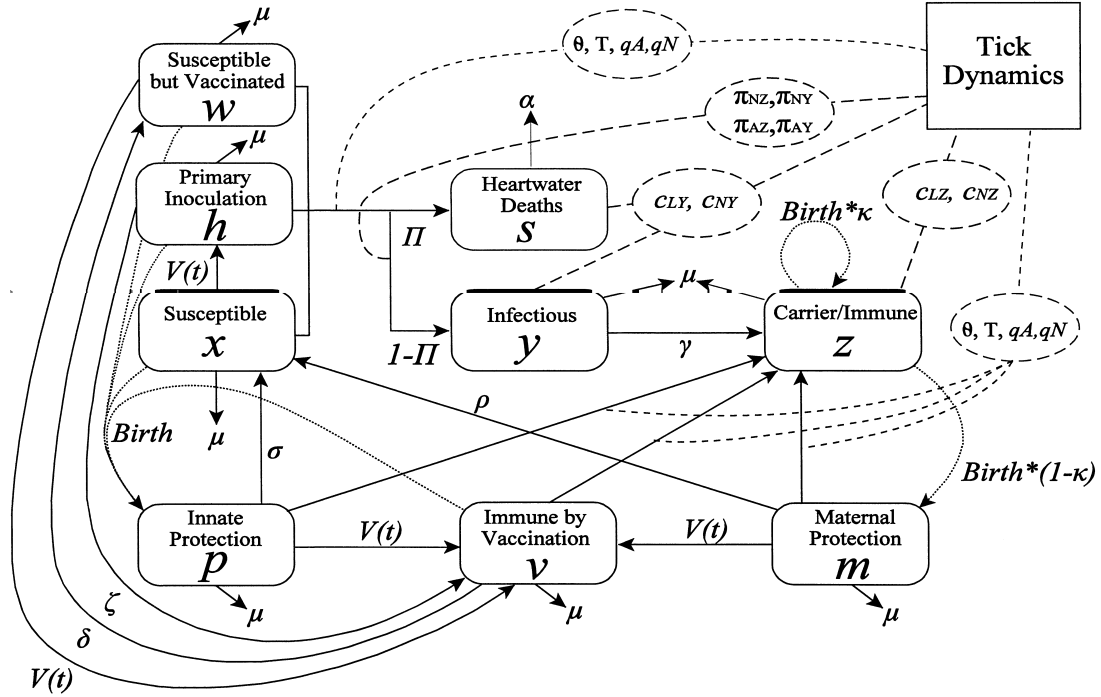
Fig. 1. Schematic representation of a model of the transmission dynamics of *C. ruminantium* infection for large-scale commercial beef herds in *A. hebraeum*-endemic areas of Zimbabwe incorporating vaccination. Solid lines indicate direction of flow, dashed lines demonstrate influence and dotted lines depict additions through birth.
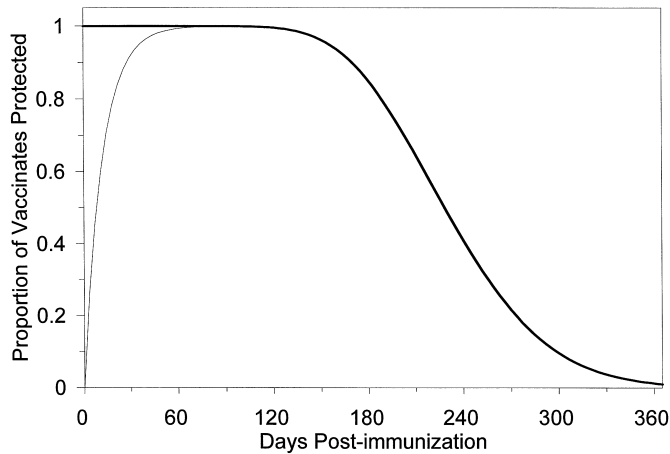
Fig. 2. The assumed time course of heartwater vaccine protection in beef cattle. The lower, thin line represents the rise in immunological response on first vaccination; the thick line represents the response on subsequent vaccinations and is superimposed over the thin line from approximately 60 days post-immunisation onwards. The median protection period is about 230 days, with virtually all individuals susceptible after one year.

become infected. These cattle remain fully susceptible to infection and hence at risk of developing fatal disease (s) should they be challenged. If animals are not exposed during the period spent in the primary inoculation class they become fully protected by virtue of vaccination (v). Thus, the proportion of animals which enter the primary inoculation category (h) from the susceptible category (x) on primary vaccination may be considered a product of the vaccine efficacy and vaccine coverage ($V(t)$).

Immune by vaccination; v. Animals within this category are protected from "clinical" (y) or lethal (s) disease. If they are infected during this period of vaccine-induced protection, they become carriers (z) without passing through a period of acute infection and are assumed to be immune for life thereafter. In addition to acquiring immunity after an induction period following vaccination (h), animals may enter the immune by vaccination category from a number of other routes. Calves born to fully susceptible dams and experiencing a limited period of innate protection (p), or calves (born to carrier dams) which were not vertically infected but which are still experiencing maternal factor protection (m), enter this category directly on primary inoculation. This is a reflection of the longer periods of innate and maternally derived resistance, relative to the induction period (Neitz and Alexander, 1941; Neitz et al., 1947; du Plessis and Malan, 1987, 1988; Deem et al., 1996a). Revaccination of vaccine-protected individuals extends the period of vaccine protection. Finally, animals previously immunised but for which disease protection has waned (w) are also assumed to enter this category directly on subsequent vaccination, in acknowledgement of the speed and magnitude of the anamnestic immune response.

Vaccinated but susceptible; w. Vaccinated individuals that have not been infected during the induction (h) or protection periods (v) return to this category after a given period of time (i.e., after the length of duration of immunity induced by the vaccine) and

then behave as the fully susceptible class (x) on infection. On subsequent vaccination, these animals become protected (v) immediately due to immunological memory.

We assumed that vaccination of animals with acute infections (y and s) and of carrier animals (z) has no effect.

2.2. Hypothetical vaccine characteristics

Detail of the assumptions regarding the vaccine characteristics are given below and in Appendix A. The induction period was incorporated as an exponential decay of susceptibility with mean duration of 15 days. Acquisition of protection on primary inoculation is represented by the thin line in Fig. 2. To approximate a natural pattern of decay of protection, we divided the vaccinated class into a series of 20 subclasses through which individuals flow sequentially. This allowed us to develop a non-exponential protection period without resorting to time delays (Gurney et al., 1985; Blythe and Anderson, 1988). The mean duration within each vaccinated subclass was 11 days. The bold line in Fig. 2 presents the resulting distribution of proportion of vaccinates protected over time post-immunisation, demonstrating near-complete loss of vaccine-related protection after one year and a median protection period of approximately 230 days. Revaccination of vaccine-protected individuals returns them to the first vaccine-protected class (v_1).

To better approximate management of commercial beef enterprises, we included vaccination as a pulse, i.e., all animals were assumed to be vaccinated at one point in time. This represents a discrete switch in the dynamic system, requiring careful incorporation into dynamic model solution. We considered pulse strategies with a frequency of either annual or semi-annual vaccination. The proportion of each category of individuals that is affected by the vaccination depends on the category (see above), the vaccination coverage applied (i.e., the proportion of at-risk animals actually vaccinated) and the vaccine efficacy (the proportion of susceptible animals protected by the vaccine when vaccinated – a property inherent in the vaccine). The overall level of protection is calculated as the product of the latter two parameters. We considered four different levels: 90%, 70%, 50% and 30%. The lowest level was included to investigate the effect of a vaccine that would, by most standards, be considered too ineffective to be used.

2.3. Vaccination strategies/scenarios

All scenarios were begun with the system at equilibrium: either infection-free or with infection. The equilibrium with infection is a function of the tick-attachment rate (TAR = number of adult ticks attaching to a host each day; represented mathematically as $T(t)$), such that there is a threshold TAR below which infection is not maintained in the populations. However, infection levels increase non-linearly with increasing TAR above the threshold. The disease shows a convex relationship with TAR, reaching a maximum at intermediate levels. Higher TARs induce an equilibrium with lower disease incidence: the endemically stable state (Fig. 3). See O'Callaghan et al. (1998) for further details and discussion.
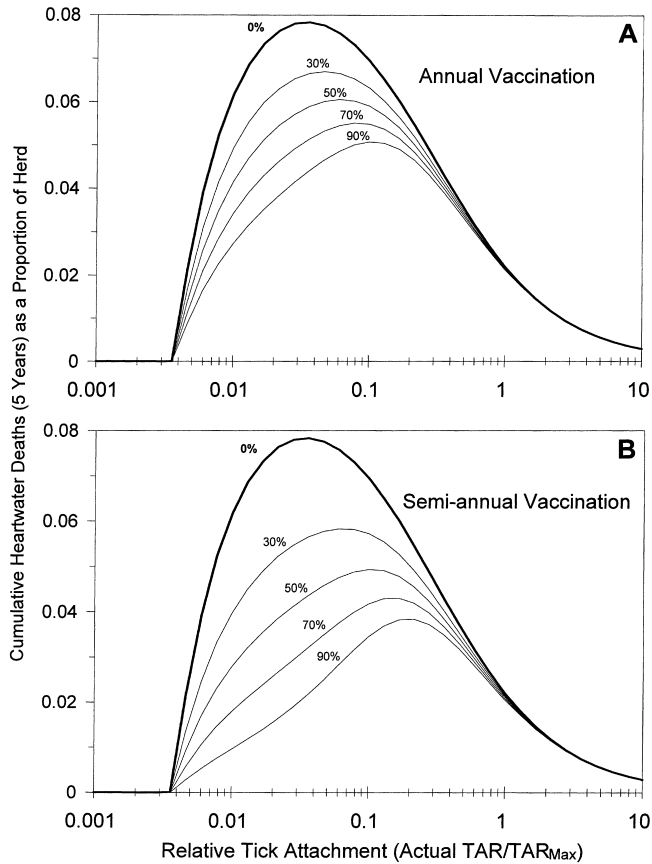
Fig. 3. Cumulative heartwater deaths over five years at equilibrium as a function of the actual tick-attachment rate relative to TAR_{Max} for (a) annual and (b) semi-annual vaccination pulses and expressed as the proportion of a beef herd. The thick line is without vaccination; the thin lines represent increasing protection levels as shown.

2.3.1. Vaccination at endemic equilibrium

After host, vector and parasite have been coexisting for some time, the populations will be at an equilibrium with respect to host and tick infection rates and disease incidence. Depending on where this endemic equilibrium occurs on the spectrum of TAR, the vaccine may be used to reduce death and disease in the absence of any change in vector challenge. We modelled this scenario by the introduction of vaccine into the equilibrium population at time zero across a range of possible TARs (from below the threshold value for maintenance to 10 times the highest rate documented in the field – see below).

2.3.2. Vaccination of a susceptible herd in the face of an epidemic

One common use of a vaccine will be to reduce disease incidence when the parasite and vector are introduced into a susceptible host population. This is the situation in parts of the highveld of Zimbabwe, where reduction in acaricide use allowed *A. hebraeum* (the
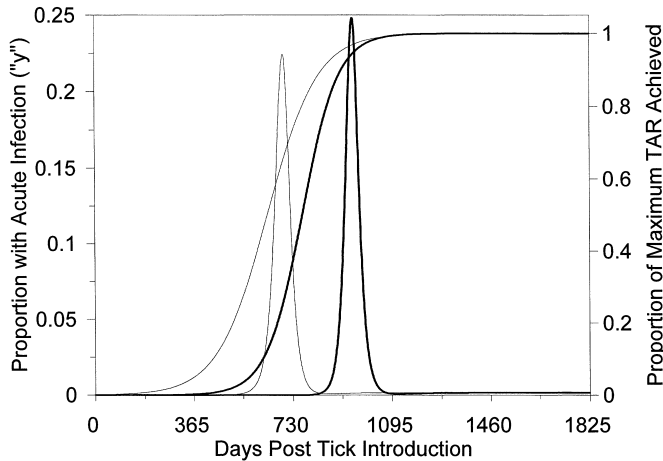
Fig. 4. The two possibilities for timing of the heartwater epidemic during the five year period caused by two different initial population sizes of invading ticks. The monotonically rising sigmoid-shaped lines represent the logistic increase in TAR as a proportion of the maximum rate (TAR$_{Max}$). The two epidemic peaks are the proportion of a beef herd with acute infection. The thin lines are the faster epidemic.

major *C. ruminantium* vector in Zimbabwe) to increase its range and resulted in increased outbreaks of heartwater (Peter et al., 1998a, b, 1999).

Much is unknown of the population dynamics of the tick vector. Consequently, we model the increase in TAR from near zero (TAR$_0$) to 0.5 adult tick-attachments per day (TAR$_{Max}$). The later was the highest TAR we observed in the absence of vector control during three years of field studies in heartwater endemic areas of Zimbabwe (unpublished data). We used a logistic function that reached 99.3% of the maximum level after three years from first introduction (Fig. 4; Appendix A). Given the lack of quantitative evidence, we believe this captured the essential pattern of an initial rapid growth in an unconstrained tick population, later slowing as it approaches an ecological-maximal carrying capacity and density-dependent mechanisms come into effect. The tick population was started at time zero with either 1/2000 or 1/200 000 of the equilibrium level (i.e., with a small number of infected ticks) when the host population was completely infection-free.

These two initial conditions gave rise to two different epidemiological patterns (Fig. 4). With the high-level introduction (the faster epidemic = the thin line), the epidemic of infection occurred while TAR was still low relative to TAR$_{Max}$. This may be considered equivalent to the situation where vector and parasite arise simultaneously in a previously naive population. With a lower initial condition (the slower epidemic = the bold line), the peak of disease occurred when the vector was at almost equilibrium density. This is essentially equivalent to introduction of the parasite when host and vector are close to equilibrium. For both epidemics, we considered that vaccination started when the incidence of heartwater reached 1/4000 cattle, and continued either annually or semi-annually from that time onwards.

2.3.3. Prophylactic vaccination of a susceptible herd

Given the availability of a vaccine, it is likely that some beef-ranching enterprises that are not currently affected by heartwater will choose to vaccinate against the possibility of introduction. Indeed, in the case when the herd is being kept heartwater-free through intensive use of acaricides, if the vaccine provides sufficient protection, it might be economical to use the vaccine to reduce reliance on acaricides. We considered the situations where a herd was vaccinated for five years (either annually or semi-annually) prior to time zero. The vector and parasite were introduced at time zero using the same assumptions as for vaccination in the face of an epidemic, giving rise to two different epidemic patterns. In both cases, once vaccination began, it continued at the same frequency.

2.4. Outcome measures

The permutation of vaccine-use scenario, epidemic pattern and vaccination frequency gives 10 combinations. In each of these we considered a five-year period starting at time zero. Because we were interested in both resultant epidemic patterns and outcomes relevant to economic analysis, we show results of both acute-disease prevalence and cumulated death over the period as proportions of the herd (see Appendix A). The principal model assumption concerning herd dynamics is that each death results in an immediate birth to keep the herd size constant. Consequently, the numerator and denominator for cumulative death are not independent and should be interpreted as the percentage losses from a herd with constant turnover of the population.

3. Results

3.1. Vaccination at endemic equilibrium

Fig. 3 shows the effect of vaccination in equilibrium situations for five different levels of protection and two different vaccination frequencies (Fig. 3(a): annual and Fig. 3(b): semi-annual) on the cumulative heartwater deaths over five years (expressed as a proportion of the herd). For both vaccination frequencies, the vaccine was most beneficial in areas of intermediate transmission where disease incidence was highest. Vaccination at either frequency had very little effect in high-transmission areas. Semi-annual vaccination (i.e., revaccination before vaccine-derived immunity wanes) was more beneficial than annual vaccination. For semi-annual vaccination, there was also an effect of decreasing returns on increasing protection; increasing protection from 30% to 50% reduced death more than increasing protection from 70% to 90%. Altering the frequency of revaccination would appear to have as great effect as changing coverage and efficacy. A vaccine of only 30% efficacy given to a whole herd produces a reduction in mortality that might be cost-effective if given semi-annually in areas of intermediate challenge.

Vaccination was never 100% effective in reducing deaths because individuals born between vaccination pulses were not protected. With our assumptions about vaccine characteristics, if all calves were successfully vaccinated prior to infection and became

infected during periods of vaccine-induced protection, deaths from heartwater would be zero.

3.2. Vaccination in the face of an epidemic

Fig. 5 shows the results of vaccinating in the face of an epidemic for different levels of vaccine protection under the assumptions of the faster-rising epidemic (Fig. 4, the thin lines) and annual (Fig. 5(a)) and semi-annual (Fig. 5(b)) revaccination. Vaccination had two effects: it reduced the size of the epidemic, and it delayed the occurrence of the peak of the epidemic. In the case of annual revaccination, this delay can result in an epidemic that occurs during a period of higher relative herd susceptibility (i.e., when vaccine protection is beginning to wane), so that the resultant epidemic is actually larger. This effect did not occur with semi-annual revaccination (Fig. 5(b)), nor under the assumption of a later epidemic regardless of revaccination frequency (data not shown).

Cumulative deaths are shown in Fig. 6. Note that cumulative deaths without vaccination almost reached 25%. The delaying effect of vaccination and lack of continued vaccine protection can result in a reduction of overall effectiveness of a
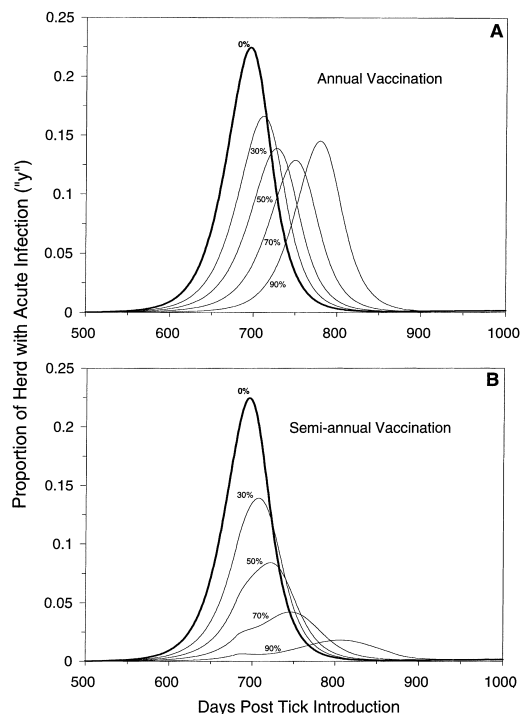

Fig. 5. The effect of heartwater vaccination in the face of an epidemic as the proportion of a beef herd with acute infection over time under the assumption of the faster epidemic (thin lines Fig. 3). The thick line shows the pattern with no vaccination. (a) Annual revaccination following first pulse vaccination with the protection levels shown. (b) Semi-annual revaccination following first pulse vaccination with the protection shown.
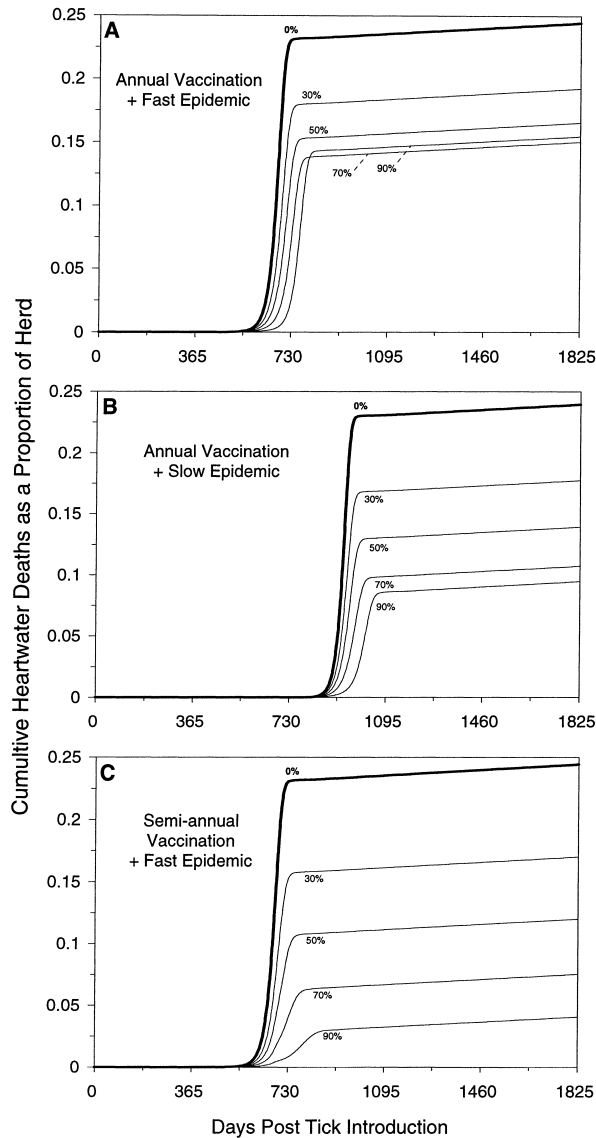
Fig. 6. The effect of heartwater vaccination in the face of an epidemic as the cumulative heartwater deaths over time in a beef herd. (a) Fast epidemic and annual revaccination (as in Fig. 5(a)). (b) Slow epidemic and annual revaccination. (c) Fast epidemic and semi-annual revaccination (as in Fig. 5(b)). The results for slow epidemic with semi-annual revaccination are qualitatively similar to Fig. 5(c).

programme with increasing vaccine protection; the cumulated deaths were higher for 90% protection than 70% protection (Fig. 6(a)). Otherwise, a similar pattern emerged as for vaccination at equilibrium, where increased protection resulted in decreasing returns in the programme effectiveness (Fig. 6(b)). Nonetheless, high coverage with a highly
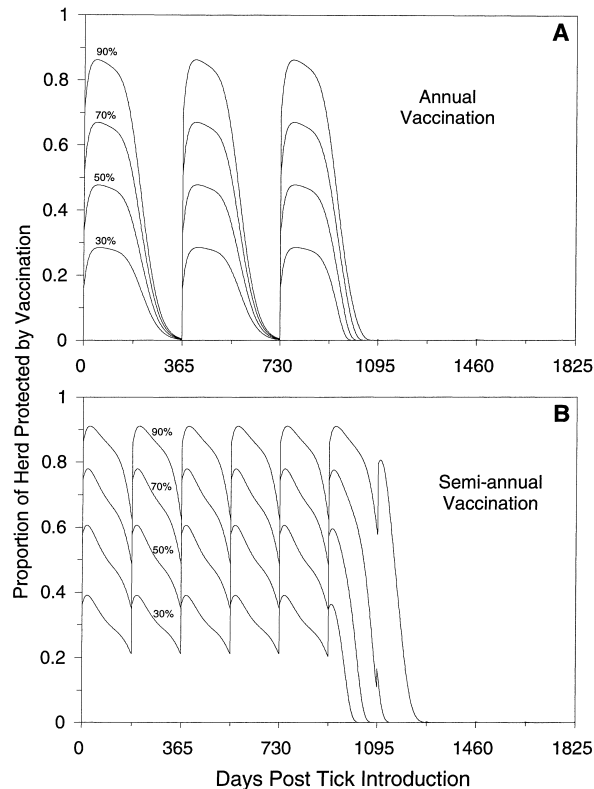
Fig. 7. The proportion of a beef herd protected by heartwater vaccination over time with (a) annual and (b) semi-annual prophylactic revaccination using the slower epidemic (thick lines Fig. 3) and protection levels as shown.

efficacious vaccine applied in the face of an epidemic with revaccination frequently enough to avoid waning of immunity can reduce cumulative deaths by a factor of 7 (Fig. 6(c)).

3.3. Prophylactic vaccination

Fig. 7 shows the changes in proportion of individuals protected over time for annual and semi-annual vaccination. The patterns show the effect of pulse vaccination on overall levels of protection from the introduction of *C. ruminantium* and its vector after five years of prophylactic vaccination. Because we assumed that each vaccination pulse was an independent event (with non-responders and/or unvaccinated animals distributed at random within the herd), a vaccine with 90% protection (e.g., vaccinating all individuals with a vaccine of 90% efficacy) can produce overall peak protection of either less than 90% or greater than 90%, depending on the frequency of revaccination. The fall in vaccine protection around day 1000 was due to infection of individuals when the epidemic ensued, as shown in Fig. 8.
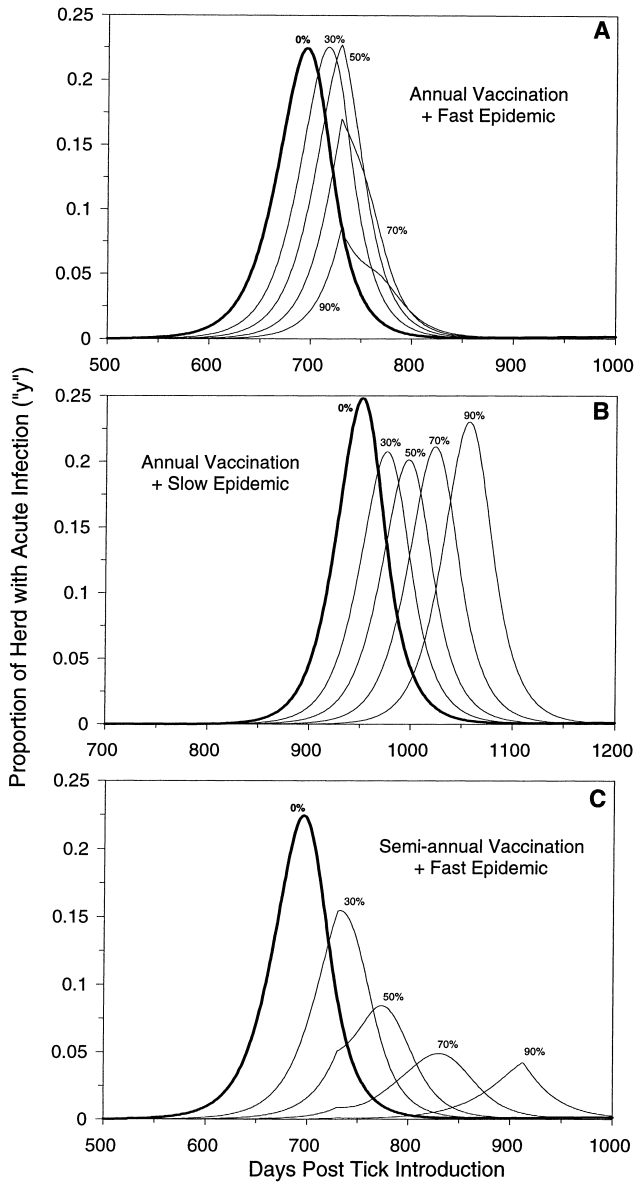
Fig. 8. The heartwater epidemic with prophylactic vaccination as the proportion of a beef herd with acute infection over time. (a) Faster epidemic with annual re-vaccination. (b) Slower epidemic with annual revaccination. (c) Faster epidemic with semi-annual revaccination. The epidemics assuming the slower epidemic with semi-annual revaccination are qualitatively similar to Fig. 5(c). Protection levels of the vaccine are as shown.

Again, the principal effects of prophylactic vaccination were reduction in size of epidemic and delay of the peak. Fig. 8 shows the epidemic of disease and Fig. 9 the cumulated deaths for annual revaccination with fast and slow epidemics and semi-annual
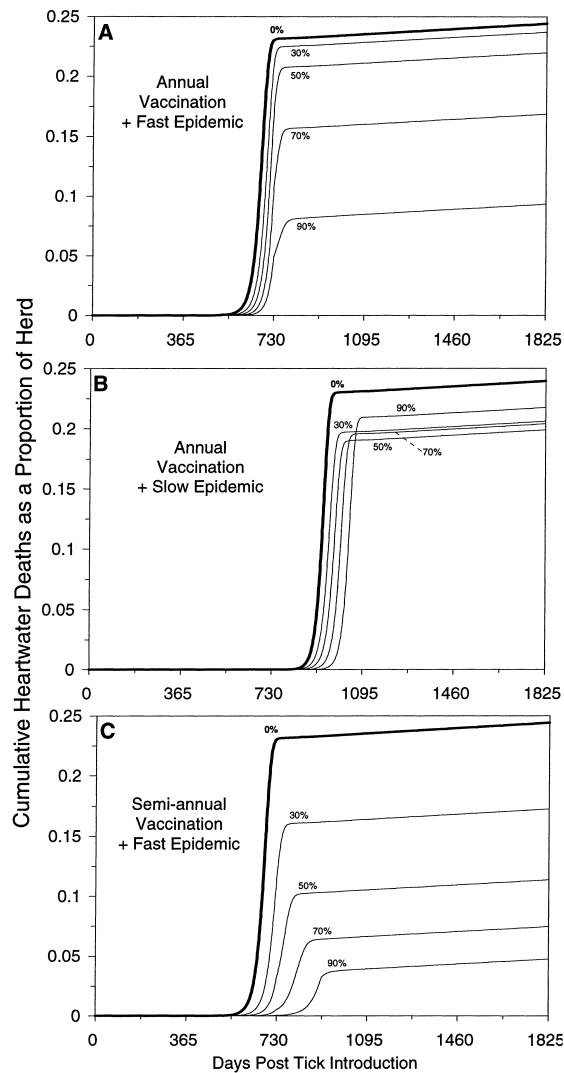
Fig. 9. Cumulative heartwater deaths in a beef herd for the epidemics shown in Fig. 8.

revaccination. Both the epidemic pattern (compare Fig. 8(a) with (b) and Fig. 9(a) with (b)), and the frequency of vaccination (compare Fig. 8(a) with (c) and Fig. 9(a) with (c)) can have greater influence on the outcome than protection levels achieved at each vaccination pulse. The situation in Fig. 8(b) and Fig. 9(b) demonstrates that the vaccine had very little effect and that the efficacy of the vaccine or proportion of vaccination coverage was virtually irrelevant.

The results are crucially determined by the interplay between timing of vaccination pulses, assumed rate of rise in TAR and duration of vaccine protection. Fig. 9(a) shows

increasing returns for increasing degrees of protection, and Fig. 9(c) shows reducing returns.

4. Discussion

We modelled the effect of introducing a vaccine with defined properties into three different epidemiological situations. Because we used varying degrees of vaccine efficacy/coverage, our results give some indication of when a vaccine might be sufficiently developed to be of value in the field. It is also evident from our results that the overall effectiveness of vaccines will differ according to how they are used in the field under different epidemiological circumstances, and that there is an interaction between efficacy (as measured in conventional challenge trials), transmission dynamics and vaccination protocol. Even relatively low vaccine efficacy and coverage combinations can have important effects on the transmission dynamics of infection during epidemics.

Not surprisingly, there is little advantage to mass vaccination and revaccination of herds at endemic equilibrium where the challenge is either very low or very high (Fig. 3). When challenge is very high, most animals are infected during periods of innate or maternally derived immunity and become immune-carriers directly (therefore avoiding death), i.e., under endemic stability (see O'Callaghan et al., 1998). However, depending on the relative costs of vaccine and value of animals, vaccination of individual calves (as a protection of individuals rather than as an attempt to modify the transmission dynamics within the population) may be a cost-effective intervention. In addition (although not modelled explicitly in this study), there is likely a role for vaccination in endemically stable situations to provide protection to newly introduced animals. In contrast, for areas with intermediate challenge (and the highest heartwater mortality risks), mass vaccination is always beneficial; the level of benefit increases with efficacy, coverage, and most importantly, revaccination frequency. The level of challenge at which peak mortality occurs is also increased (Fig. 3(b)), indicating that the combination of vaccination and tick population control (including acaricide use) might increase benefits and should be explored further.

The results of prophylactic vaccination and vaccination in the face of an epidemic indicate that it may always be beneficial, provided that vaccine-induced immunity is maintained by sufficiently frequent revaccination over the course of the epidemic. This result holds for different forms of the epidemic (in terms of the relationship between tick-attachment rate and *C. ruminantium* infection prevalence), suggesting that acaricide use in the face of an epidemic will not interact with the effect of vaccination. More specifically, a reduction in vector-control efforts (designed to achieve an invariant and relatively high level of tick challenge where ecoclimatically possible), combined with the use of vaccination in an appropriate protocol, might allow a transition to endemic stability with minimal heartwater morbidity and mortality. A vaccine with 30% efficacy is capable of reducing the total deaths during the epidemic by approximately 40% (Fig. 6(c) and Fig. 9(c)) due to the reduced intensity of infection in ticks caused by fewer acutely infected cattle. For a vaccine of sufficiently low cost, this could ultimately be

cost-effective. However, increasing the efficacy results in a reduced marginal effect (for sufficient levels of revaccination), so that time and resources spent in development of the vaccine above a particular level of efficacy may be uneconomic.

When revaccination is not performed sufficiently frequently to maintain immunity, some surprising results can occur due to the delaying effect on the epidemic. This reaction can be sufficient to render vaccination ineffective (Fig. 6(a) and Fig. 8(a) and (b)) and to make vaccines which are apparently efficacious at the individual level less proficient in preventing disease in the population. The situation would become more complicated if seasonal effects (principally host demographics and TAR) were included in the model. It is possible that our results for vaccination at equilibrium could be altered by these considerations. Recent consideration of the dynamic effects of pulse vaccination in children show that the birth rate largely determines the frequency of pulses required (Nokes and Swinton, 1997). The effect of seasonality is generally important in tick-borne infections, particularly in southern Africa, and must be considered further.

5. Conclusions

Our principal conclusion is that the timing of vaccine use (in epidemic situations), the degree of challenge (at equilibrium) and the frequency of revaccination all can have greater effect on population protection than the efficacy of vaccine. It is not enough to develop a vaccine that protects individual animals; its circumstances of use within herds must be considered carefully. The important factors are the rate and time of increase of rate of infection (measured here by TAR) and degree of vaccine protection during greatest rate of infection. The use of vaccine changes the rate of infection – usually reducing it so that epidemics are slower and smaller (due to the reduced capacity of carrier animals to infect ticks compared to animals with acute infection and the reduced lethality of those tick infections derived from carriers) (see O'Callaghan et al., 1998 and Appendix A). Thus, where a vaccine is to be used in an integrated control programme designed to ultimately achieve endemic stability, vaccination may have to be maintained at an adequate frequency for a relatively prolonged period. Also the use of a vaccine in the face of an epidemic can be beneficial, given the right circumstances.

It is clear that vaccines of the type considered here should be developed with the epidemiological and transmission-dynamics situations in which they are to be deployed as major consideration. In particular, the characteristics of efficacy and duration of protection are somewhat compensatory. However, the investigation of the effects of introducing a new mass vaccination programme can only be conducted through large, expensive field trials or by predictive modelling.

Acknowledgements

Appendix A

The text contains the principal assumptions used to incorporate vaccination and the situations when it is used within the dynamic model. O'Callaghan et al. (1998) provide a full description of the infection transmission model, however, a summary of pertinent details of the original model and the modifications made to include vaccination is presented herein (see Fig. 1).The host population is initially divided into six mutually exclusive categories of infection status:

Susceptible to infection; x. Naive animals that have not been exposed to *C. ruminantium* previously, are susceptible to infection and at risk of developing fatal disease (s).

Acutely infected but will survive; y. Acutely infected animals (resulting from infection of susceptible animals – x) that are highly infectious to ticks and will recover to become carriers of infection (z).

Acutely infected but will die; s. Acutely infected animals (resulting from infection of susceptible animals – x) that are highly infectious to ticks but will die from heartwater.

Carriers; z. Animals that have recovered from infection, are able to infect ticks at a much reduced capacity and are immune to further disease. Carriers arise from infection of either susceptible animals (through the y category) or directly from infection of animals that are protected from disease by maternal factors (m) or innate factors (p). Animals infected vertically from their dams also immediately become carriers themselves.

Maternal factor protected; m. Calves born to carrier dams (but not vertically infected) which are protected against disease for a limited period.

Age-specific protection; p. Calves born to susceptible dams possess an innate protection which lasts for a shorter period of time than that derived from maternal factors. If calves are not infected during the period of protection afforded by either the m or p categories, they become fully susceptible (x).

The rates at which animals recover from infection ($\gamma = 1/20$/day), die from heartwater ($\alpha = 1/15$/day) or from "natural" mortality due to causes other than heartwater ($\mu = 1/4$/year), or lose maternal factor ($\rho = 1/30$/day) and innate protection ($\sigma = 1/10$/day), are constant.

The host population size is given the nominal value of unity, so that the sub-populations represent the proportions in each infection stage; consequently, the model outcome units, where appropriate, are per head of cattle.

The assumptions made in the infection dynamics of *C. ruminantium* in a cattle population give rise to a set of deterministic time-delayed non-linear ordinary differential equations:

$$
\begin{aligned}
\frac{\mathrm{d}m}{\mathrm{d}t} &= b(t)z(1 - \kappa) - m[\mu + \rho + \lambda(t)] - V(t)m, \\
\frac{\mathrm{d}p}{\mathrm{d}t} &= b(t)(1 - z) - p[\mu + \sigma + \lambda(t)] - V(t)p, \\
\frac{\mathrm{d}x}{\mathrm{d}t} &= \rho m + \sigma p - x[\lambda(t) + \mu] - V(t)x, \\
\frac{\mathrm{d}y}{\mathrm{d}t} &= \lambda(t)[1 - \Pi(t)](x + r + w) - y(\gamma + \mu), \\
\frac{\mathrm{d}s}{\mathrm{d}t} &= \Pi(t)\lambda(t)(x + r + w) - s\alpha, \\
\frac{\mathrm{d}z}{\mathrm{d}t} &= b(t)z\kappa + \gamma y - \mu z + \lambda(t)[m + p + \bar{v}],
\end{aligned}
\tag{A.1}
$$

where $V(t)$ is the vaccination function, $b(t)$ the birth rate, $\Pi(t)$ the proportion of infections that give rise to fatal infections and $\lambda(t)$ is the rate of infection.

The birth rate is chosen to ensure that the population remains constant over time (i.e., exactly equals death from all causes):

$$b(t) = \mu(x + y + z + m + p + r + \bar{v} + w) + \alpha s. \tag{A.2}$$

The rate of infection of hosts and the proportion of host infections which are lethal are functions of the tick-attachment rate, the stage of tick providing the infection (i.e., nymph or adult) and the source of infection to the tick (i.e., acute-stage infection or carrier).

Amblyomma hebraeum is an ixodid tick with three developmental instars (larva, nymph and adult). Each larva or nymph detaches from the host following completion of feeding, moults and the subsequent instar quests for a further host. Only nymphae and adults are able to transmit infection, and only larvae and nymphae can become infected. The probability of acquisition of infection of a tick feeding successfully on an infected host (c) was considered constant for each combination of feeding instar (either larvae (L) or nymphae (N)) and the host infection category (either acutely infected (y) or carrier (z)), represented as subscripts ($c_{Ly} = 0.5$, $c_{Lz} = 0.01$, $c_{Ny} = 0.8$, $c_{Nz} = 0.1$). The proportion of ticks that become infected during feeding at a previous stage (r) may be similarly subscripted and expressed by the equations:

$$\begin{aligned}
r_{Ly}(t) &= c_{Ly}[y + s], \\
r_{Lz}(t) &= c_{Lz}z, \\
r_{Ny}(t) &= K_{Ny}x + c_{Ny}[y + s], \\
r_{Nz}(t) &= K_{Nz}x + c_{Nz}z.
\end{aligned} \tag{A.3}$$

Under the assumption that the tick population is at equilibrium, the prevalence of infectious ticks (K) within the questing stages of adult (A) and nymphae (N), but also differentiated by source of infection (subscripted as above), may be calculated:

$$\begin{aligned}
\dot{K}_{Ny} &= (\omega_N + \eta_N)\{r_{Ly}(t - \phi_L) - K_{Ny}\} \\
\dot{K}_{Nz} &= (\omega_N + \eta_N)\{r_{Lz}(t - \phi_L) - K_{Nz}\} \\
\dot{K}_{Ay} &= (\omega_A + \eta_A)\{r_{Ny}(t - \phi_N) - K_{Ay}\} \\
\dot{K}_{Az} &= (\omega_A + \eta_A)\{r_{Nz}(t - \phi_N) - K_{Az}\},
\end{aligned} \tag{A.4}$$

where ω_A and ω_N are the host-finding rates of questing adults and nymphae ($\omega_A = \omega_N = 1/100/\text{day}$), η_A and η_N are the death rates of questing adults and nymphae ($\eta_A = \eta_N = 1/100/\text{day}$), ϕ_L is the moulting delay for larva $\rightarrow$ nymph ($=30$ days) and ϕ_N is the moulting delay for nymph $\rightarrow$ adult ($=60$ days). Essentially, the questing stages act as distributed time delays for infection in the tick populations; i.e., the prevalence of infection of questing stages at one time is a sum of all surviving infectious ticks.

The rate of infection can now be defined as:

$$\lambda(t) = T(t)(q_A[K_{Ay} + K_{Az}] + \theta q_N[K_{Ny} + K_{Nz}]), \tag{A.5}$$

which is the sum of infection proportions from the four different classes of infectious tick ($K_{Ay}(t)$, $K_{Az}(t)$, $K_{Ny}(t)$, $K_{Nz}(t)$) weighted by the ratio of nymphal : adult tick-attachments ($\theta = 10$), the probabilities of susceptible host infection by each instar ($q_A = 0.9$ and $q_N = 0.8$ for adults and nymphae, respectively) and the adult tick-attachment rate ($T(t)$).

The proportion of animals that die from heartwater is determined by the source of the infection, so that:

$$\Pi(t) = \frac{1}{\theta q_N + q_A} \left\{ \frac{[\pi_{Ny} K_{Ny} + \pi_{Nz} K_{Nz}] \theta q_N}{K_{Ny} + K_{Nz}} + \frac{[\pi_{Ay} K_{Ay} + \pi_{Az} K_{Az}] q_A}{K_{Ay} + K_{Az}} \right\}, \tag{A.6}$$

which is a weighted average of case-fatality proportions (π), combining the lethality of infection from the four permutations of different instars and sources of infection ($\pi_{Nz} = 0.1$, $\pi_{Ny} = 0.2$, $\pi_{Az} = 0.3$, $\pi_{Ay} = 0.4$).

The additional equations required for the vaccination compartments are as follows:

$$\begin{aligned}
\frac{dh}{dt} &= V(t)x - \zeta h - \lambda(t)h - \mu h, \\
\frac{dv_1}{dt} &= \zeta h + V(t)(\bar{v} + w + m + p) - v_1(\lambda(t) + \delta + \mu + V(t)), \\
\frac{dv_i}{dt} &= \delta v_{i-1} - v_i(\lambda(t) + \delta + \mu + V(t)) \quad \text{for } i = 2, \ldots, 20, \\
\frac{dw}{dt} &= \delta v_{20} - \mu w - \lambda(t)w - V(t)w,
\end{aligned} \tag{A.7}$$

where

$$\bar{v} = \sum_{i=1}^{20} v_i \tag{A.8}$$

is the total proportion of vaccine protected animals. The parameter ζ is the rate of development of immunity ($=1/15$/day), and δ is the rate of transfer between protection classes ($=1/11$/day).

The outcome measures shown in Figs. 4, 5–9 are prevalence of acute disease, y, as a measure of morbidity, and the cumulated heartwater death:

$$\int_{t=0}^{t=5\,\text{yr}} \alpha s(t) \, dt. \tag{A.9}$$

For those scenarios where an increasing tick-attachment rate (TAR) is required, the growth in the tick-attachment rate is calculated as:

$$T(t) = \frac{\text{TAR}_{\text{Max}}}{1 + \left(\dfrac{\text{TAR}_{\text{Max}}}{\text{TAR}_0} - 1 \right) \exp(-gt)}, \tag{A.10}$$

where TAR_{Max}, the maximum, equilibrium attachment rate, is 0.5 adult ticks/host/day. TAR_0 is the initial rate (at time 0) and is $1/200\,000$ (slower epidemic) or $1/2000$ (faster epidemic) of TAR_{Max}. The parameter, g, is calculated to give the required rise (i.e., 99.3% of maximum three years after introduction):

$$g = -\ln\left(\frac{0.007}{(0.993\text{TAR}_{\text{Max}}/\text{TAR}_0) - 1} \right) \frac{1}{1095}. \tag{A.11}$$

References

Anderson, R.M., May, R.M., 1991. Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford.

Bezuidenhout, J.D., Prozesky, L., du Plessis, J.L., van Amstel, S.R., 1994. Heartwater. In: Coetzer, J.A.W., Thomson, D.G., Tustin, R.C. (Eds.), Infectious Diseases of Livestock, With Special Reference to Southern Africa, vol. I. Oxford University Press, Cape Town, pp. 351–370.

Blythe, S.P., Anderson, R.M., 1988. Distributed incubation and infectious periods in models of the transmission dynamics of the human immunodeficiency virus (HIV). IMA J. Math. Appl. Med. Biol. 5, 1–19.

Burridge, M.J., 1997. Heartwater: an increasingly serious threat to the livestock and deer populations of the United States. In: Proceedings of 101st Annual Meeting of United States Animal Health Association. Spectrum Press, Richmond, VA, USA, pp. 582–597.

Camus, E., Barre, N., Martinez, D., Uilenberg, G., 1996. Heartwater (Cowdriosis). A Review, 2nd ed. Office International des Epizooties, Paris, France.

Deem, S.L., Donachie, P.L., Norval, R.A.I., 1996a. Colostrum from dams living in a heartwater-endemic area influences calfhood immunity to Cowdria ruminantium. Vet. Parasitol. 61, 119–132.

Deem, S.L., Norval, R.A.I., Yonow, T., Peter, T.F., Mahan, S.M., Burridge, M.J., 1996b. The epidemiology of heartwater – establishment and maintenance of endemic stability. Parasitol. Today 12, 402–405.

du Plessis, J.L., Malan, L., 1987. The non-specific resistance of cattle to heartwater. Onderstepoort J. Vet. Res. 54, 333–336.

du Plessis, J.L., Malan, L., 1988. Susceptibility to heartwater of calves born to non-immune cows. Onderstepoort J. Vet. Res. 55, 235–237.

du Plessis, J.L., van Gas, L., Olivier, J.A., Bezuidenhout, J.D., 1989. The heterogeneity of Cowdria ruminantium stocks: cross-immunity and serology in sheep and pathogenicity to mice. Onderstepoort J. Vet. Res. 56, 195–201.

Grenfell, B.T., Dobson, A.P. (Eds.), 1996. Ecology of Infectious Disease in Natural Populations. Cambridge University Press, Cambridge.

Gurney, W.S.C., Nisbet, R.M., Blythe, S.P., 1985. The systematic formulation of models of stage-structured populations. Lecture Notes in Biomath. 68, 474–494.

Lawrence, J.A., Norval, R.A.I., 1979. A history of ticks and tick-borne diseases of cattle in Rhodesia. Rhodesian Vet. J. 10, 28–40.

Mahan, S.M., Andrew, H.R., Tebele, N., Burridge, M.J., Barbet, A.F., 1995. Immunization of sheep against heartwater with inactivated Cowdria ruminantium. Res. Vet. Sci. 58, 46–49.

Mahan, S.M., Kumbula, D., Burridge, M.J., Barbet, A.F., 1998. The inactivated Cowdria ruminantium vaccine for heartwater protects against heterologous strains and against laboratory and field challenge. Vaccine 16, 1203–1211.

Martinez, D., Maillard, J.C., Coisne, S., Sheikboudou, C., Bensaid, A., 1994. Protection of goats against heartwater acquired by immunisation with inactivated elementary bodies of Cowdria ruminantium. Vet. Immunol. Immunopathol. 67, 153–163.

Martinez, D., Perez, J.M., Sheikboudou, C., Debus, A., Bensaid, A., 1996. Comparative efficacy of Freund's and Montanide ISA 50 adjuvants for the immunisation of goats against heartwater with inactivated Cowdria ruminantium. Vet. Parasitol. 67, 175–184.

Medley, G.F., 1994. The transmission dynamics of Theileria parva. In: Perry, B.D., Hansen, J.W. (Eds.), Modelling Vector-Borne and other Parasitic Diseases: Proceedings of a Workshop Organized by ILRAD in Collaboration with FAO, ILRAD, Nairobi, Kenya, 23–27 November, 1992. International Laboratory for Research on Animal Diseases, Nairobi, Kenya.

Medley, G.F., Perry, B.D., Young, A.S., 1993. Preliminary analysis of the transmission dynamics of Theileria parva in eastern Africa. Parasitology 106, 251–264.

Morzaria, S.P., 1996. Monitoring the efficiency of immunization against theileriosis caused by Theileria parva. In: Irvin, A.D., McDermott, J.J., Perry, B.D. (Eds.), Epidemiology of Ticks and Tick-borne Diseases in Eastern, Central and Southern Africa: Proceedings of a Workshop, Harare, Zimbabwe, 12–13 March, 1996. International Livestock Research Institute, Nairobi, Kenya, pp. 103–114.

Mukhebi, A.W., Chamboko, T., O'Callaghan, C.J., Peter, T.F., Kruska, R.L., Medley, G.F., Mahan, S.M., Perry, B.D., 1999. An assessment of the economic impact of heartwater (*Cowdria ruminantium* infection) and its control in Zimbabwe. Prev. Vet. Med. 39, 173–190.

Mukhebi, A.W., Perry, B.D., Kruska, R., 1992. Estimating economic losses caused by theileriosis and the economics of its control in Africa. Prev. Vet. Med. 12, 73–85.

Neitz, W.O., Alexander, R.A., 1941. The immunisation of calves against heartwater. J. South African Vet. Med. Assoc. 12, 103–111.

Neitz, W.O., Alexander, R.A., Adelaar, T.F., 1947. Studies on immunity to heartwater. Onderstepoort J. Vet. Res. 21, 243–249.

Nokes, D.J., Swinton, J., 1997. The control of childhood viral infections by pulse vaccination. IMA J. Math. Appl. Med. Biol. 12, 29–53.

Norval, R.A.I., 1978. The effects of partial breakdown of dipping in African areas in Rhodesia. Rhodesian Vet. J. 9, 9–16.

Norval, R.A.I., 1979. Tick infestations and tick-borne diseases in Zimbabwe/Rhodesia. J. South African Vet. Assoc. 50, 289–292.

Norval, R.A.I., Andrew, H.R., Yunker, C.E., Burridge, M.J., 1992. Biological processes in the epidemiology of heartwater. In: Fivaz, B.H., Petney, T.N., Horak, I.G. (Eds.), Tick Vector Biology: Medical and Veterinary Aspects. Springer, London, pp. 71–86.

Norval, R.A.I., Lawrence, J.A., 1979. The control of heartwater in Zimbabwe/Rhodesia. Rhodesian J. Agric. Res. 76, 161–165.

O'Callaghan, C.J., Medley, G.F., Peter, T.F., Perry, B.D., 1998. Investigating the epidemiology of heartwater (*Cowdria ruminantium* infection) by means of a transmission dynamics model. Parasitology 117, 49–61.

Perry, B.D., Deem, S.L., Medley, G.F., Morzaria, S.P., Young, A.S., 1992. The ecology of *Theileria parva* infections of cattle and the development of endemic stability. In: Munderloh, U.G., Kurtti, T.J. (Eds.), At the Host-Vector Interface: An Agenda for Research, Proceedings of the First International Conference on Tick-borne Pathogens. Department of Entomology and Minnesota Extension Service, University of Minnesota College of Agriculture, Saint Paul, MN, USA.

Perry, B.D., Young, A.S., 1995. The past and future roles of epidemiology and economics in the control of tick-borne diseases of livestock in Africa: the case of theileriosis. Prev. Vet. Med. 25, 107–120.

Peter, T.F., Perry, B.D., O'Callaghan, C.J., Medley, G.F., Shumba, W., Madzima, W., Burridge, M.J., Mahan, S.M., 1998a. The distribution of heartwater in the highveld of Zimbabwe: 1980–1997. Onderstepoort J. Vet. Res. 65, 177–187.

Peter, T.F., Perry, B.D., O'Callaghan, C.J., Medley, G.F., Shumba, W., Madzima, W., Burridge, M.J., Mahan, S.M., 1998b. Distribution of the vectors of heartwater, *Amblyomma hebraeum* and *Amblyomma variegatum* (Acari: Ixodidae) in Zimbabwe. Exp. Appl. Acarol. 22, 1–16.

Peter, T.F., Perry, B.D., O'Callaghan, C.J., Medley, G.F., Shumba, W., Madzima, W., Burridge, M.J., Mahan, S.M., 1999. The threat of heartwater to ruminants in the highveld of Zimbabwe. Zimbabwe J. Agric. Res., in press.

Radley, D.E., Brown, C.G.D., Cunningham, M.P., Kimber, C.D., Musisi, F.L., Payne, R.C., Purnell, R.E., Stagg, D.A., Young, A.S., 1975. East Coast Fever. 3. Chemoprophylactic immunization of cattle using oxytetracycline and a combination of theilerial strains. Vet. Parasitol. 1, 51–60.

Tjornehoj, K., Lawrence, J.A., Kafuwa, P.T., Whiteland, A.P., Chirema, B.A.R., 1997. Immunisation of smallholder dairy cattle against anaplasmosis and babesiosis in Malawi. Tropical Anim. Health Prod. 29, 77–82.

van der Merwe, L., 1987. The infection and treatment method of vaccination against heartwater. Onderstepoort J. Vet. Res. 54, 489–491.

Young, A.S., Groocock, C.M., Kariuki, D.P., 1988. Integrated control of ticks and tick-borne diseases of cattle in Africa. Parasitology 96, 403–432.